REMARKS

Claims 29-60 are pending in this application. Claims 1-28 have been cancelled without prejudice or disclaimer. Claims 29-60 have been newly added.

Claims 1-28 have been cancelled for the sole reason of advancing prosecution. Applicants, by cancelling any claims herein, make no admission as to the validity of any rejection made by the Examiner against any claims. Applicants reserve the right to reassert the full scope of any claim cancelled herein later in prosecution and/or in a continuing application.

Claims 29-60 have been newly added. Support for newly added claims 29-60 can be found throughout the specification and claims as originally filed. No new matter has been added.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 3 of the Official Action, claims 1-7 and 9-26 have been rejected under 35 USC § 102(b) as being anticipated by Fuisz.

The Examiner asserts that Fuisz teaches each element of each of claims 1-7 and 9-26.

Claims 1-7 and 9-26 have been cancelled without prejudice or disclaimer, thus rendereing this rejection moot as to these claims. Further, it is submitted that in view of the remarks herein, new claims 29-60 are novel in view of Fuisz.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v.*

Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. R*ichardson v. Suzuki Motor Co.,* 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond,* 15 USPQ2d 1566 (Fed. Cir. 1990).

Independent claim 29 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; and (c) a formulation effective in reducing the pH in a menstruating vagina or in a tampon inserted therein to below pH 5.5, the formulation comprising 30-100 wt% of glycolide; optionally, 15-97 wt% of a solid organic acid; and optionally, 5-30 wt% of a wetting agent, based on the total weight of the formulation." Claims 29-49 each depend, directly or indirectly, from independent claim 29.

Independent claim 50 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; and (c) a formulation effective in reducing the pH in a menstruating vagina or in the catamenial tampon inserted therein to below pH 5.5 within one hour or less from the time of insertion, comprising 30-100% by weight of glycolide; optionally, 97-15% by weight of a solid organic acid; and optionally, 5-30% of a wetting agent." Claims 51-52 each depend directly from independent claim 50.

Independent claim 53 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; (c) a polymeric support provided between the inner core and the outer layer; and (d) a formulation deposited on the polymeric support,

the formulation effective in reducing the pH in a menstruating vagina or in the catamenial tampon inserted therein to below pH 5.5, comprising 30-100% by weight of glycolide, optionally, 97-15% by weight of a solid organic acid, and optionally, 5-30% of a wetting agent. Claims 54-60 each depend, directly or indirectly, from independent claim 53.

All of newly added claims 29-60 require a catamenial tampon comprising, in part, an inner core, an outer layer and a formulation. Fuisz does not teach or suggest a catamenial tampon comprising an inner core, an outer layer and a formulation. Accordingly, Fuisz does not teach each and every element of each of newly added claims 29-60. Thus, Applicants assert that newly added claims 29-60 are novel in view of Fuisz.

Further, the Examiner refers to specific polymers disclosed in Fuisz and marketed under the Medisorb and Biodel trademarks. These polymers are disclosed in Fuisz (column 7, lines 5-17) as a "lactide/glycolide polymer" and "include Medisorb 100 L believed to be 100% glycolide" or "Medisorb 5050 DL believed to be a copolymer of 50% lactide and 50% glycolide". Applicants assert that this disclosure is ***irrelevant*** to the presently claimed subject matter.

Fuisz is referring to polymers, ***not*** monomers (*see* col. 6, line 22 to col. 7, line 17). Glycolide and lactide are monomers, ***not*** polymers. The structural, chemical and physical properties of monomers and polymers differ, sometimes radically. For example, the monomer styrene is toxic, while the polymer polystyrene is not toxic. In the present case, glycolide and lactide are ***cyclic dimers*** of glycolic acid and lactide acid, respectively (*see* the present specification at page 2, lines 31-33). However, upon undergoing polymerization, the ring is cleaved at the alkyl-oxygen bond yielding a ***linear*** polycarbonate (*see* New Methods for Polymer Synthesis [ed. W.J. Mijs], (1992), pages 50-51 (Attachment

A); Principles of Polymerization [ed. George Odian], (2004), pages 585-586(Attachment B)). Fuisz discloses Medisorb which is a co-polymer containing lactoyl and glycoyl units (*see* the enclosed Fact Sheet published by the owner of the rights to Medisorb(Attachment C)).

In addition, the delivery time of drugs incorporated in the Medisorb matrix (*see* enclosed abstract of Ramstack, et al (Attachment D)) is measured in ***days*** or ***weeks,*** while in the present case, delivery is constant and complete within ***hours*** – thus the high molecular weight PLGA or Medisorb is ***not suitable for use in the tampon*** presently claimed since it degrades too slowly. Thus, a disclosure of the polymer (Medisorb) does not anticipate nor render obvious the use of the monomer (glycolide). The Examiner is respectfully request to ***expressly address*** the foregoing ***arguments and citations*** if this rejection is to be maintained.

In view of the foregoing, it is submitted that Fuisz does not teach each and every element of present claims 29-60 as required for anticipation under 35 USC § 102. Thus, it is submitted that claims 29-60 are novel in view of Fuisz.

II. At page 4 of the Official Action, claims 1-26 have been rejected under 35 USC § 102(e) as being anticipated by Meyers.

The Examiner asserts that Meyers teaches each element of each of claims 1-26.

Claims 1-26 have been cancelled without prejudice or disclaimer, thus rendereing this rejection moot as to these claims. Further, it is submitted that in view of the remarks herein, new claims 29-60 are novel in view of Meyers.

The test for anticipation is whether each and every element as set forth is found,

either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. R*ichardson v. Suzuki Motor Co.,* 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond,* 15 USPQ2d 1566 (Fed. Cir. 1990).

Independent claim 29 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; and (c) a formulation effective in reducing the pH in a menstruating vagina or in a tampon inserted therein to below pH 5.5, the formulation comprising 30-100 wt% of glycolide; optionally, 15-97 wt% of a solid organic acid; and optionally, 5-30 wt% of a wetting agent, based on the total weight of the formulation." Claims 29-49 each depend, directly or indirectly, from independent claim 29.

Independent claim 50 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; and (c) a formulation effective in reducing the pH in a menstruating vagina or in the catamenial tampon inserted therein to below pH 5.5 within one hour or less from the time of insertion, comprising 30-100% by weight of glycolide; optionally, 97-15% by weight of a solid organic acid; and optionally, 5-30% of a wetting agent." Claims 51-52 each depend directly from independent claim 50.

Independent claim 53 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; (c) a polymeric support provided between the

inner core and the outer layer; and (d) a formulation deposited on the polymeric support, the formulation effective in reducing the pH in a menstruating vagina or in the catamenial tampon inserted therein to below pH 5.5, comprising 30-100% by weight of glycolide, optionally, 97-15% by weight of a solid organic acid, and optionally, 5-30% of a wetting agent. Claims 54-60 each depend, directly or indirectly, from independent claim 53.

All of newly added claims 29-60 require a catamenial tampon comprising, in part, an inner core, an outer layer and a formulation. Meyers does not teach or suggest a catamenial tampon comprising an inner core, an outer layer and a formulation. Accordingly, Meyers does not teach each and every element of each of newly added claims 29-60. Thus, Applicants assert that newly added claims 29-60 are novel in view of Meyers.

The Examiner points out that Myers discloses tampons comprising a film (paragraph [0122]). However, the film of Myers uses polymers of glycolide, while the presently claimed subject matter is directed uses the glycolide monomer. Furthermore, the tampon of Myers ***does not*** have the structure of the tampon of the present claims (an inner core comprising an absorbent material, and an outer layer comprising a liquid permeable material). Finally, the tampon of Myers uses a pH modulated film, i.e. a film whose properties are modulated by pH (*see* the end of paragraph [0122]), while the formulation of the tampon of the present claims modulates or reduces the pH in the vagina or tampon. Thus, Myers does not anticipate new claims 29-60. Accordingly, it is submitted that new claims 29-60 are novel in view of Meyers.

Myers discloses dissolvable films produced through a selection of a pH modulated polymer system (paragraph [0013]). Examples of film-forming polymers which may be used

in Meyers include polymers marketed under the Medisorb and Biodel trademarks [0102]. Please *see* the discussion above regarding the same polymers disclosed in the Fuisz reference.

Applicants assert that this disclosure regarding Medisorb and Biodel is ***irrelevant*** to the presently claimed subject matter.

Meyers is referring to polymers, ***not*** monomers. Glycolide and lactide are monomers, ***not*** polymers. The structural, chemical and physical properties of monomers and polymers differ, sometimes radically. For example, the monomer styrene is toxic, while the polymer polystyrene is not toxic. In the present case, glycolide and lactide are ***cyclic dimers*** of glycolic acid and lactide acid, respectively (*see* the present specification at page 2, lines 31-33). However, upon undergoing polymerization, the ring is cleaved at the alkyl-oxygen bond yielding a ***linear*** polycarbonate (*see* New Methods for Polymer Synthesis [ed. W.J. Mijs], (1992), pages 50-51; Principles of Polymerization [ed. George Odian], (2004), pages 585-586). Meyers discloses Medisorb which is a co-polymer containing lactoyl and glycoyl units (*see* the enclosed Fact Sheet published by the owner of the rights to Medisorb).

In addition, the delivery time of drugs incorporated in the Medisorb matrix (*see* enclosed abstract of Ramstack, et al) is measured in ***days*** or ***weeks,*** while in the present case, delivery is constant and complete within ***hours*** – thus the high molecular weight PLGA or Medisorb is ***not suitable for use in the tampon*** presently claimed since it degrades too slowly. Thus, a disclosure of the polymer (Medisorb) does not anticipate nor render obvious the use of the monomer (glycolide). The Examiner is respectfully request

to ***expressly address*** the foregoing ***arguments and citations*** if this rejection is to be maintained.

In view of the foregoing, it is submitted that new claims 29-60 are novel in view of Meyers.

III. At page 6 of the Official Action, claims 1-26 have been rejected under 35 USC § 103(a) as being unpatentable over Kluger et al. in view of Myers.

The Examiner asserts that "...it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to modify Kluger et al. formulation by further replacing lactide by glycolide. Meyers discloses that lactide can be replaced by glycolide and vice versa."

Claims 1-26 have been cancelled without prejudice or disclaimer, thus rendereing this rejection moot as to these claims. Further, it is submitted that in view of the remarks herein, new claims 29-60 are patentable over Kluger et al. in view of Myers.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U. S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would

have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*.

Independent claim 29 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; and (c) a formulation effective in reducing the pH in a menstruating vagina or in a tampon inserted therein to below pH 5.5, the formulation comprising 30-100 wt% of glycolide; optionally, 15-97 wt% of a solid organic acid; and optionally, 5-30 wt% of a wetting agent, based on the total weight of the formulation." Claims 29-49 each depend, directly or indirectly, from independent claim 29.

Independent claim 50 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; and (c) a formulation effective in reducing the pH in

a menstruating vagina or in the catamenial tampon inserted therein to below pH 5.5 within one hour or less from the time of insertion, comprising 30-100% by weight of glycolide; optionally, 97-15% by weight of a solid organic acid; and optionally, 5-30% of a wetting agent." Claims 51-52 each depend directly from independent claim 50.

Independent claim 53 is directed to "A catamenial tampon for insertion in a human vagina, comprising: (a) an inner core comprising an absorbent material; (b) an outer layer comprising a liquid permeable material; (c) a polymeric support provided between the inner core and the outer layer; and (d) a formulation deposited on the polymeric support, the formulation effective in reducing the pH in a menstruating vagina or in the catamenial tampon inserted therein to below pH 5.5, comprising 30-100% by weight of glycolide, optionally, 97-15% by weight of a solid organic acid, and optionally, 5-30% of a wetting agent. Claims 54-60 each depend, directly or indirectly, from independent claim 53.

The combination of Kluger and Myers does not render the presently claimed subject matter obvious since neither Kluger nor Myers teaches the use of the monomer glycolide. Please *see* the above arguments, regarding polymers versus monomers, incorporated herein by reference in their entirety. The Examiner further states that "Myers discloses that lactide can be replaced by glycolide and vice versa" (page 10). Applicants strongly traverse this statement. The Examiner has ***not*** shown how Myers discloses this. Please *see* the arguments filed in our previous response of June 2, 2009, particularly pages 14-17, incorporated herein by reference in their entirety. The Examiner has not at all addressed the arguments of June 2, 2009.

In view of the foregoing, it is submitted that nothing in Kluger and Meyers, taken alone or together, renders claims 29-60 obvious within the meaning of 35 USC § 103.

Thus, it is submitted that claims 29-60 are patentable over the combination of Kluger and Meyers.

Applicants again emphasize that the present subject matter is directed to a formulation comprising ***glycolide***, and ***not*** a polymer thereof. The Examiner is again requested to expressly address the foregoing should this rejection be maintained.

The Examiner is ***again requested to cite authority*** that would establish that glycolide and lactide are interchangeable, and that glycolide can be used in combination with lactide or separately in a formulation without any physiological effect to the composition, should this rejection be maintained.

The data set forth in the Examples of the present specification clearly establishes that lactide and glycolide ***are not interchangeable,*** and that the use of glycolide exhibits unexpectedly superior results over the use of lactide.

Applicants again assert that ***glycolide and lactide are not interchangeable***. Rather, they are ***different*** cyclic esters having ***different*** chemical properties.

Glycolide is a completely different molecule than lactide. Glycolide has a different molecular structure and different properties than lactide. Glycolide is a cyclic dimer of two glycolic acid molecules, while lactide is a cyclic dimer of two lactic acid molecules. The main difference between lactide and glycolide, is that ***glycolide is hydrophilic*** and ***lactide is hydrophobic***. This is due to the absence, in glycolide, of the two pendant methyl groups which are present in lactide. Thus, glycolide undergoes hydrolysis (and converts into two glycolic acid molecules) much more efficiently and quickly than lactide, for example, during tampon usage. This well-know difference in properties of lactide and glycolide is used to tailor the degradation kinetics of many known artificial implants and medical devices, the

most familiar of which are the degradable sutures. Such sutures can be made of copolymers synthesized from lactide (hydrophobic) and glycolide (hydrophilic), the ratio between the two components in the polymer dictates the degradation rate of the polymer, which should be approximately at the rate of tissue healing. In view of the foregoing, it is clear that glycolide and lactide have ***significantly different properties*** and are thus, ***not*** interchangeable.

Glycolide is a cyclic dimer of glycolic acid. *See* the Dictionary of Organic Compounds, 1,4-dioxane-2,5-dione; Names, Synonyms, and Structures of Organic Compounds, page 488; and SciFinder Scholar, 1,4-dioxane-2,5-dione. A copy of each of which was submitted with the Amendment and Response filed on March 20, 2008. *See also* www.sigma-aldrich.com "glycolide" (printout submitted with the Amendment and Response filed on March 20, 2008) and www.bio-invigor.com "GLY-S-001-1" (printout submitted with the Amendment and Response filed on March 20, 2008). Further, U.S. Patent Nos. 3,457,280 and 3,435,008 (submitted with the Amendment and Response filed on March 20, 2008) both describe that two molecules of glycolic acid "may condense with the elimination of two molecules of water to produce glycolide, a six-membered ring of the formula $C_4H_4O_4$…." U.S. Patent No. 5,374,743 describes at col. 1, lines 9-11, "The monomer used is lactide or glycolide which are cyclic dimmers of lactic acid or glycolic acid and which are prepared from lactic acid or glycolic acid." *See also* U.S. Patent Nos. 6,891,048 and 7,235,673 submitted with the Amendment and Response filed on March 20, 2008.

In addition, lactide is a cyclic dimer of lactic acid. *See* http://en.wikipedia.org/wiki/Lactide.

These differences in properties between lactide and glycolide result in surprising advantages using glycolide rather than lactide to reduce pH, as supported by the results

described in the Examples set forth in the present specification.

Thus, the specification provides ample proof of the superiority of glycolide over lactide, and further evidences that ***glycolide and lactide are NOT interchangeable***. This feature is ***not*** taught or suggested by ***any of the cited references***, taken alone or in combination. Again, should this rejection be maintained, the Examiner is requested to expressly address this argument as well as the data set forth in the Examples of the present specification.

Kluger et al. do not teach or suggest glycolide at all, let alone the advantages of using glycolide over lactide. In fact, the term "glycolide" ***does not appear at all*** in Kluger et al.

One of ordinary skill in the art would have no reason to use glycolide for the solid organic acid polymer based on the disclosure of Kluger et al. Kluger et al. do not teach or suggest a "formulation ***effective in reducing the pH in a menstruating vagina or in a tampon inserted therein*** to below pH 5.5" either comprising or consisting of glycolide. Therefore, whether alone or in combination, none of the cited references teach or suggest the presently claimed subject matter.

CONCLUSION

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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Attachment A

New Methods for Polymer Synthesis

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epithioethane and carbon disulfide with triethylamine as a catalyst proceeds at room temperatures to give an alternating copolymer in 63% yield for 4 days.[82] In this case, concomitant formation of ethylene trithiocarbonate has been observed. The copolymerization with $Hg(SC_4H_9)_2$ gives a copolymer with a rather low thiocarbonate content (50–70%).[83] In the copolymerizations initiated with organometallic compounds such as $Al(C_2H_5)_3$, $Zn(C_2H_5)_2$, and $Cd(C_2H_5)_2$, the thiocarbonate content of the produced copolymer falls down considerably to the range of 0–18%.

Copolymerization of episulfides with elemental sulfur with an eight-membered ring takes place in aromatic hydrocarbon solvents below the floor temperature for radical homopolymerization of elemental sulfur. $CdCO_3$ and alkali metal thiophenoxide–crown ether systems are representative catalysts, which allow the formation of copolymer with the number-average molecular weight and sulfur content up to 50,000 and 85%, respectively.[84] The copolymers of episulfides and elemental sulfur are very reluctant to undergo depolymerization, and form transparent films by casting from solution.

2.4. LACTONES AND RELATED MONOMERS

Lactones with four-, six-, and seven-membered rings can be polymerized anionically, but the polymerization of five-membered lactones with anionic initiators has never been successful. Polymerization of the four-membered cyclic ester, β-lactone, usually proceeds by ring cleavage at the alkyl–oxygen bond, differently from lactones with a larger ring, the growing species being a carboxylate [Eq. (2.14)]. Polymerization of lactones with a larger ring proceeds by the normal mode of cleavage of the ester bond, i.e., acyl–oxygen bond scission [Eq. (2.15)]. Cyclic dimers of α-hydroxy acids such as glycolide and lactide, six-membered cyclic carbonates, and morpholinediones are the related monomers that can be also polymerized with nucleophilic initiators.


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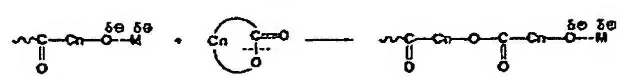
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n = 4, 5

2.4.1. Lactones

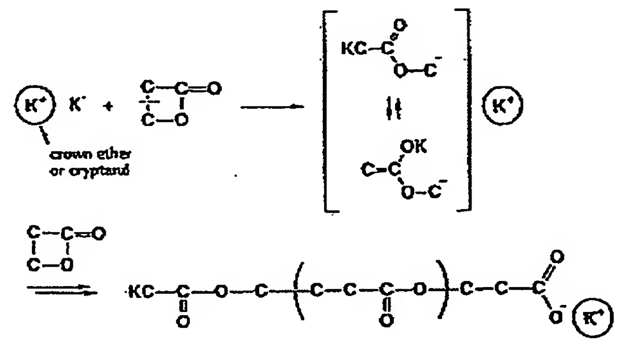
2.4.1.1. Syntheses of Polyesters with Uniform Molecular Weight

For the synthesis of polyesters of uniform, controlled molecular weight, aluminum porphyrin is one of the most effective initiators and is capable of

initiating living polymerizations of four-,[11,85,86] six-,[87] and seven-membered lactones.[88] The growing species of the polymerization of four-membered lactones with aluminum porphyrin initiator is a (porphinato)aluminum carboxylate,[85] while the polymerizations of higher lactones proceed via (porphinato)aluminum alkoxides as the growing species.[87,89] Furthermore, these polymerizations are of an immortal character in the presence of appropriate protic compounds. Accordingly, polyesters of uniform molecular weight are formed with the number of polymer molecules equal to the sum of the molecules of the aluminum porphyrin and protic compound.[19,88] Tailored block copolymers consisting of polyesters and polyethers can also be synthesized by sequential polymerizations of lactones and epoxides using aluminum porphyrin initiators. Living poly(methyl methacrylate) prepared with alkylaluminum porphyrins brings about the polymerization of a six-membered lactone to afford a poly(methacrylic ester)–polyester block copolymer with uniform block lengths.[39]

Bimetallic μ-oxo alkoxides with the formula $(RO)_2AlOZnOAl(OR)_2$[90] and dialkylaluminum alkoxides[91] are also very effective initiators for the living polymerization of a seven-membered lactone such as ε-caprolactone. Use of $(RO)_2AlOZnOAl(OR)_2$ reacted with polystyrene or polybutadiene carrying a hydroxyl end group as initiator for the polymerization of ε-caprolactone affords the corresponding polyvinyl–polyester block copolymers.[92]

Alkali metal solutions containing crown ether or cryptand have been reported to initiate the polymerization of four-membered lactones such as β-propio- and β-butyrolactones, where the lactone enolate species are formed at the initial stage, and polymerization has been proposed to be initiated via C—C bond cleavage of the monomer [Eq. (2.16)].[93,94]



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2.4.1.2. Syntheses of Stereoregular Polyesters

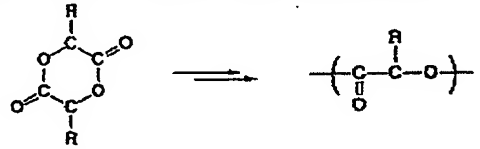
Stereoselective polymerization of lactones to give crystalline polyesters has attracted some attention in relation to the structure of naturally occurring poly(α-hydroxy ester).[75]

Enantioselective polymerizations of racemic α,α-disubstituted β-propiolactones such as α-ethyl-α-methyl-β-propiolactone and α-methyl-α-propyl-β-propiolactone have been attempted with the $ZnEt_2/(R)$-(−)-$(CH_3)_3CCH(OH)CH_2OH$ system as initiator at room temperature. The k_S/k_R ratios of 1.02–1.07 and 1.25, respectively, have been observed.[95]

For the polymerization of β-substituted β-propiolactones, the $ZnEt_2/H_2O$ (1/1) system is a more favorable initiator than the $AlEt_3/H_2O$ (1/1) system in terms of the crystallinity of the produced polymers.[96] Poly(β-butyrolactone) prepared with the $ZnEt_2/H_2O$ (1/1) system gives, upon fractionation with chloroform, a crystalline polymer as an insoluble fraction, whose X-ray diffraction pattern is virtually identical to that of the naturally occurring poly(β-hydroxybutyrate). The polymerization of β-butyrolactone with the $AlEt_3/H_2O$/epichlorohydrin (1-chloro-2,3-epoxypropane) system affords a polyester with a very high crystallinity.[97] The polymerization of racemic β-butyrolactone with the $ZnEt_2/(R)$-(−)-$(CH_3)_3CCH(OH)CH_2OH$ system is one of the most successful examples of enantioselective polymerization of β-substituted lactones. The unreacted monomer recovered at 84% conversion is rich in the (S)-enantiomer with 46% ee.[98] The methanol-insoluble fraction of the produced polymer, as determined by ^{13}C NMR, contains 72% isotactic diad sequences. Systematic studies on the polymerization of a series of β-substituted β-propiolactones with coordinate anionic initiators such as $AlEt_3/H_2O$/epichlorohydrin at 60 °C indicate that the crystallinity of the produced polymer tends to become low when the monomer bears a bulky substituent such as the *tert*-butyl or trichloromethyl group.[97] Additionally, the mode of ring opening of four-membered lactone has been studied in the case of polymerization of (R)-benzyl malolactonate initiated with triethylamine. It was demonstrated that the polymerization proceeds via alkyl–oxygen bond cleavage with inversion of the configuration of the asymmetric carbon atom to give poly((S)-malic acid benzyl ester).[99]

2.4.2. Cyclic Dimer of α-Hydroxy Acids (Glycolide and Lactide)

Glycolide and lactide, cyclic dimers of α-hydroxy acids (10), can be polymerized with anionic initiators to give polyesters [Eq. (2.17)], which are



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(2.17)

of practical importance for biomedical applications owing to their inherent biodegradability. Representative anionic and coordinate anionic initiators for the polymerization of these monomers include quaternary ammonium or phosphonium salts, aluminum isopropoxide, and dibutyltin dimethoxide, the latter two giving high-molecular-weight polyesters.[100] For the synthesis of poly(lactide) (10, R = CH_3) with narrow molecular-weight distribution, aluminum porphyrin initiators are effective.[32] A typical example is the polymerization of D-lactide with (tetraphenylporphinato)aluminum alkoxide with the mole ratio of 100 in CH_2Cl_2 at 100 °C, which proceeds to 94% conversion in 96 h to give a polymer with M_n and M_w/M_n of 16,400 and 1.12, respectively. In this case, M_n of the produced polymer increases linearly with conversion, retaining the M_n/M_w ratio of 1.1, and the number of polymer molecules relative to the number of initiator molecules remains constant, close to 1.0. In the presence of a protic chain transfer agent such as methanol, the polymerization of lactide with aluminum porphyrin initiator is of an immortal character. Thus, poly(lactide) with uniform molecular weight is formed with the number of polymer molecules more than that of the aluminum porphyrin initiator.[101] It should be of further interest to note that the sequential immortal polymerizations of δ-valerolactone and lactide afford the corresponding polyester–poly(lactide) block copolymer of uniform block length. Bimetallic μ-oxo alkoxides $[(RO)_2AlOZnOAL(OR)_2]$ have also been reported to be effective as initiators for the synthesis of poly(lactone)–poly(lactide) block copolymers.[102]

2.4.3. Cyclic Carbonates (1,3-Dioxan-2-Ones)

Polymerization of ethylene carbonate, a five-membered cyclic carbonate, is accompanied by considerable decarboxylation reaction, resulting in the formation of a copolymer of ethylene oxide and ethylene carbonate.[103] Metallic initiators such as butyllithium, alkali metal carbonates, dialkyltin alkoxides, and zirconium alkoxides, and organic bases such as aromatic amines and phosphines have been used. The highest mole fraction of ethylene carbonate units (45–49%) have been attained by using dialkyltin alkoxides and aromatic phosphines as initiators.

In sharp contrast, six-membered cyclic carbonates (11) undergo anionic ring-opening polymerization without decarboxylation under appropriate conditions, giving poly(trimethylene carbonate)s in excellent yields [Eq. (2.18)]. An example is shown by the polymerization of 5,5-dimethyl-1,3-dioxan-2-one (11; R^1, R^2 = CH_3, 0.74 M) with sec-butyllithium (2.5 ×

70

Attachment B

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PRINCIPLES OF POLYMERIZATION

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5

PRINCIPLES OF POLYMERIZATION
Fourth Edition

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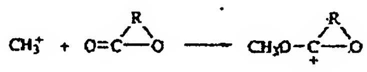
CONTENTS

oxonium ion followed by propagation through acyl–oxygen cleavage. However, polymer end-group analysis combined with trapping of propagating centers by reaction with triphenylphosphine indicates that this is not the mechanism. Initiation involves attack of a positive center on the exocyclic oxygen (the more basic oxygen) to form a dioxocarbocation (XLVIII). For example, for initiation by methyl carbocation derived from $CH_3OSO_2CF_3$ or $(CH_3)_2I^+SbF_6^-$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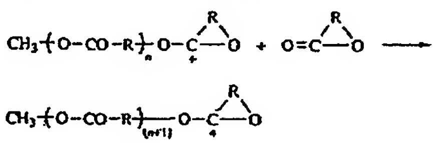
XLVIII

Propagation follows in a similar manner with alkyl–oxygen cleavage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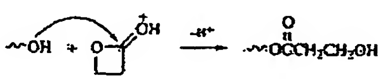
Cationic polymerization is not nearly as useful as anionic polymerization for synthesizing high-molecular-weight polyesters. The cationic route appears to be limited by intramolecular transesterification (cyclization) as well as other chain transfer to polymer reactions (including hydride and proton transfers) although there are few details in the literature. However, molecular weights in the 100,000 range have been observed for the highly reactive monomer β-propiolactone. The highly strained β-propiolactone undergoes a mixture of alkyl–oxygen and acyl–oxygen cleavages under some reaction conditions.

Cationic ROP of lactones in the presence of an alcohol proceeds by an activated monomer mechanism similar to that for cyclic ethers (Sec. 7-2b-3-b) [Endo et al., 2002; Lou et al., 2002]. Propagation proceeds by nucleophilic attack of the hydroxyl end group of a propagating chain on protonated (activated) monomer: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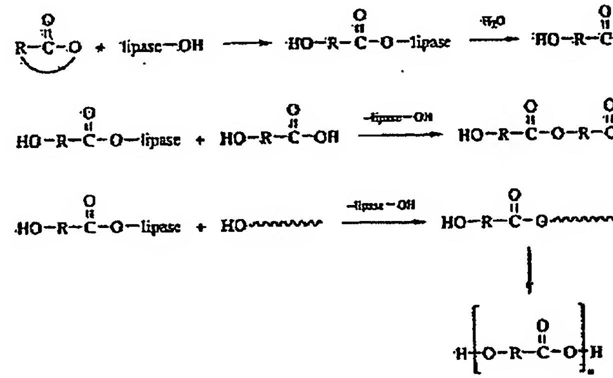
AM polymerization offers the potential for suppressing side reactions and achieving living polymerization with the ability to control MW and achieve high molecular weights.

7-5c Enzymatic Polymerization

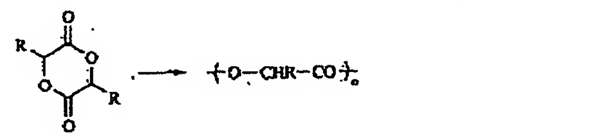
Lipases catalyze the polymerization of lactones [Duda et al., 2002; Gross et al., 2001; Kobayashi, 1999; Kobayashi et al., 2001]. The reaction mechanism is similar to that for the enzymatic polymerization of hydroxyacids (Sec. 2-17a-2). Lipase reacts with lactone to produce enzyme-activated hydroxyacid and some of the latter reacts with water to produce hydroxyacid (Eqs. 7-81). Hydroxyacid and enzyme-activated hydroxyacid react to initiate polymerization (Eq. 7-82). Propagation proceeds by nucleophilic attack of

the hydroxyl end group of the propagating chain on the enzyme-activated hydroxyacid (Eq. 7-83a).


(7-81)
(7-82)
(7-83a)
(7-83b)

7-5d Other Cyclic Esters

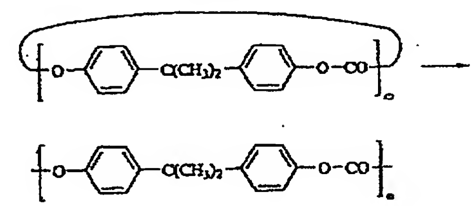
Polymerization and copolymerization of the two 1,4-dioxane-2,5-diones (dilactones), glycolide and lactide (XLIX with R = H and CH_3, respectively) proceeds using anionic initiators;


(7-84)

XLIX

cationic initiators are not as useful [Bero et al., 1990; Chamberlain et al., 2001; Chisholm et al., 2001; Kowalski et al., 1998; Kricheldorf and Kreiser-Saunders, 1990; Kricheldorf et al., 1987a,b, 2000; Leenslag and Pennings, 1987; Shibasaki et al., 2000; Stridsberg et al., 2000]. The polymerization rates are generally lower than those for lactones. Polylactide is of interest because it is both biocompatible and biodegradable. It has been used for absorbable sutures and has the potential for other biomedical applications such as drug delivery.

Polymerization of a cyclic carbonate ester yields a linear polycarbonate [Kuhling et al., 1989; Rokicki, 2000]. For example, the cyclic oligomer (m = 2–20 in Eq. 7-85) of the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carbonate derived from bisphenol A, 2,2′-bis(4-hydroxyphenyl)propane, offers an alternate route to polycarbonates other than step polymerization of bisphenol A with phosgene or ester interchange with diphenyl carbonate (Sec. 2-8e) [Brunelle et al., 1989; Stewart, 1989].

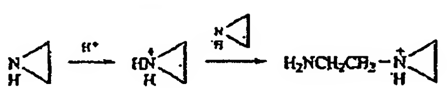
The ROP route to polycarbonates offers potential advantages relative to the step polymerization process. One advantage is that higher MW can be more easily achieved. ROP, especially with anionic initiators, proceeds as a living system and MW is determined by conversion and the ratio of monomer to initiator. MW control in step polymerization is dependent on stoichiometric ratio and conversion. Molecular weights as high as 100,000–300,000 are reported for the ROP, while the highest MWs achieved by step polymerization are 40,000–60,000. It is more difficult to achieve the very high conversions needed in step polymerization to reach the 10^5-MW range than to control the monomer–initiator ratio in ROP. Another advantage of the ROP process is the absence of by-products, which allows the use of reactive processing techniques in which cyclic monomer is directly polymerized into final objects by extrusion or molding. ROP as an alternate to step polymerization is also being studied for other high-performance polymers such as polyesters, polyamides, and polyetherimides. The ROP route is viable when the cyclic oligomer can be synthesized and polymerized in high yield.

7-6 NITROGEN HETEROCYCLICS

7-6a Cyclic Amines

Cyclic amines (referred to as *imines*) are polymerized by acids and other cationic initiators [Goethals, 1984, 1989a,b; Hauser, 1969; Kubisa, 1996; Tomalia and Killat, 1985]. The 3-membered imines (IUPAC: aziridines) are the most studied of the cyclic amines. Polyethyleneimine [IUPAC name: poly(iminoethylene)] had been commercially available and used in the treatment of paper and textiles. It is no longer available in the United States because of the high toxicity of the monomer.

The high degree of ring strain results in an extremely rapid polymerization for ethyleneimine. Initiation involves protonation or cationation of ethyleneimine followed by nucleophilic attack by monomer on the iminium $C{-}N^+$ bond. Propagation follows in the same manner. The propagating species is an iminium ion, and the reaction is analogous to the cationic polymerization of cyclic ethers. Extensive branching occurs during polymerization as evidenced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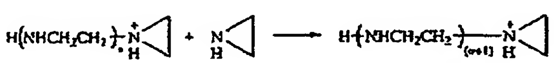

(7-87)

by the presence of primary, secondary, and tertiary amine groups in the approximate ratio 1 : 2 : 1. Tertiary amine groups result from intermolecular nucleophilic attack of secondary amine nitrogens in polymer repeat units on iminium propagating centers. This reaction simultaneously increases the primary amine group content of a polymer chain. The detailed mechanism is quite complicated since there are many equilibria present involving proton transfers among the different types of amine groups present.

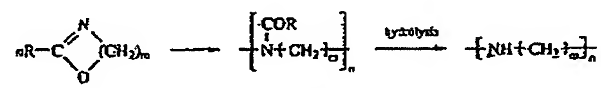
Polyethyleneimine is also extensively cyclized as a result of intramolecular nucleophilic attack of primary and secondary amines on the iminium group. This results in cyclic oligomer as well as polymer molecules containing large-sized rings as part of their structure.

Substitution on the aziridine ring hinders polymerization [Bakloutí et al., 1989; Van de Velde, 1986]. The 1,2- and 2,3-disubstituted aziridines do not polymerize; 1- and 2-substituted aziridines undergo polymerization, but the yield of polymer relative to low-molecular-weight linear and cyclic oligomers and the molecular weight of the polymer depend on the substituent (both electronic and steric effects are important).

Cationic polymerization of 4-membered imines (IUPAC: azetidines) generally follows the same patterns as the aziridines [Matyjaszewski, 1984a,b; Muhlbach and Schulz, 1988]. Imines are generally unreactive toward anionic polymerization presumably because of the instability of an amine anion (which would constitute the propagating species). The exception occurs with *N*-acylaziridines as a result of the electron deficiency of the nitrogen coupled with the highly strained 3-membered ring.

7-6b Other Nitrogen Heterocyclics

Various *endo*-imino cyclic ethers (L) undergo cationic polymerization to yield poly(*N*-acylalkyleneimine)s (LI). The most widely studied monomers are the 2-substituted 2-oxazolines ($m = 2$) (also referred to as *2-substituted-1,3-oxazolin-2-enes*) [Culbertson, 2002;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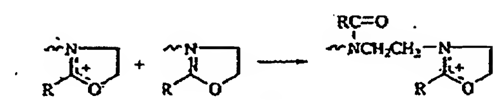
L LI LII

Goethals, 1989a,b; Kobayashi and Saegusa, 1984, 1986; Kobayashi and Uyama, 2002; Kobayashi et al., 1990a,b; Kubisa, 1996; Tomalia and Killat, 1985]. Propagation proceeds via nucleophilic attack of monomer on the C—O bond of an oxazolinium ion: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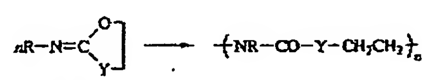
LI can be hydrolyzed to the corresponding polyamine LII. This is the only route to linear polyethyleneimine ($m = 2$) [Tanaka et al., 1983]. The polymerization of ethyleneimine yields a highly branched and cyclized product.

exo-Imino cyclic compounds (LIII) such as iminocarbonates ($Y = O$), 2-imino-1,3-oxazolidines ($Y = NR$), and 2-iminotetrahydrofurans ($Y = CH_2$) have also been polymerized:


(7-90)

LIII

An alternate approach to forming polymers by ring opening of 2-oxazolines involves the 2-mercaptoalkyl-2-oxazoline LIV, which polymerizes to LVII on heating [Gunatillake

Attachment C

fact sheet

MEDISORB® MICROSPHERES TECHNOLOGY

What is Medisorb®?

Medisorb is Alkermes' proprietary technology that enables novel formulations of pharmaceuticals by providing controlled, extended release of medication over time.

How does the Medisorb technology work?

In this technology, medication is encapsulated in microspheres made of a medical-grade polymer called polylactide co-glycolide (PLG). Each microsphere is about one-tenth of a millimeter in size, roughly equivalent to the diameter of a human hair.

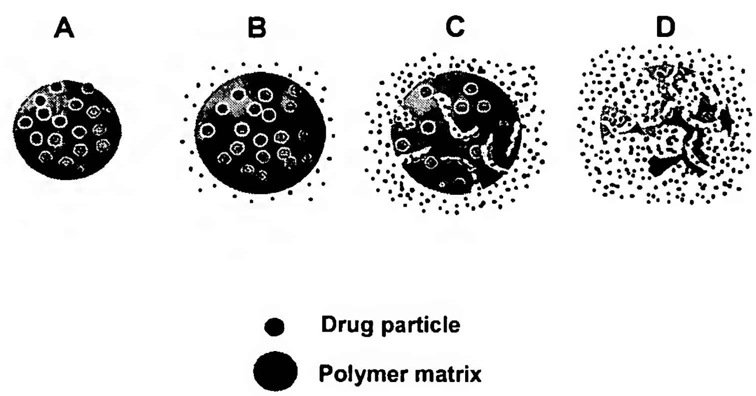
PLG is a common, biodegradable polymer with a history of safe human use in sutures, bone plates and extended-release pharmaceuticals.

Over time, the PLG polymer breaks down into lactic acid and glycolic acid, which are completely metabolized by the body and eliminated as carbon dioxide and water, thereby releasing the medication.

What happens when you inject into the body a long-acting medication using Medisorb technology?

Upon injection, the microspheres (A) begin to absorb water almost immediately, leading to a swelling of the microspheres (B). This process begins a phase in which a small amount of medication at or near the surface of the microspheres is released.

Over time water slowly breaks down the polymer structure allowing medication to release, resulting in a sustained supply of medication (C). The polymer matrix eventually breaks down and is eliminated from the body as carbon dioxide and water (D).



How does Alkermes use this injectable extended-release technology?

Alkermes' proprietary, injectable extended-release technology enables us to develop treatments that sustain effective levels of medication in the body over a prolonged time period. We have two commercial products based on this technology, RISPERDAL® CONSTA® and VIVITROL® and we are applying aspects of the technology to some of our development candidates, including exenatide once weekly.

Alkermes' extended-release technology is distinguished by:

- Clinically-proven extended-release of medication from microspheres in humans
- Demonstrated safety and tolerability in human clinical trials
- Potential to improve patient adherence to therapy, especially where extended-release dosage administration is an important factor for the selection of a medication for treatment
- Broad applicability to small molecules, peptides and proteins
- Demonstrated manufacturing capability at laboratory scale, pilot scale and commercial manufacturing scale, in compliance with cGMPs
- Ability to achieve a customized extended-release profile lasting from days to months

Attachment D

Risperdal CONSTA™: Prolonged-Release Injectable Delivery of Risperidone using Medisorb® Microsphere Technology

J. M. Ramstack[1], G. P. Grandolfi[1], E. Mannaert[2], P. D'Hoore[3], R. A. Lasser[4]

[1]*Development, Alkermes, Inc.,* [2]*Pharmacokinetics,* [3]*Full Development Teams, Johnson & Johnson Pharmaceutical Research and Development,* [4]*Medical Affairs, Janssen Pharmaceutica, Inc.*

Purpose. Long-acting antipsychotic drug delivery options are limited to painful oil-based intramuscular injections of typical antipsychotics. The purpose of this work was to develop a prolonged-release injectable form of risperidone, an atypical antipsychotic, for delivery with an aqueous vehicle. We report on the encapsulation of risperidone into polymeric microspheres using poly (d,l-lactide-co-glycolide), a common, biodegradable medical copolymer.
Methods. Risperidone microspheres are manufactured using a water-based solvent extraction process. Microspheres (sterile dry powder) are suspended in an aqueous diluent for administration. *In vitro* performance was characterized by drug release, polymer molecular weight, and visual assessment. *In vivo* data were collected from human subjects over a 13-week period.
Results. Microspheres contain ~38% risperidone loading, representing 95% encapsulation efficiency, with a homogeneous distribution of drug and a consistent particle size (25-150 μm). During the initial phase of *in vitro* drug release, controlled primarily by diffusion, a slight amount of drug (≤3.5%) at the surface of the microspheres is released within 24-hours, followed by a latent period of ~3 weeks. The major portion of drug release, controlled primarily by copolymer erosion, occurs during weeks 4-6. Polymer molecular weight decreases from ~90 to ~20 kD during the latent period, after which the rate of decay decreases with approximately ≤10 kD remaining after six weeks. The *in vivo* release profile confirms the *in vitro* profile including a very small initial release (<1%), followed by a latent period. Plasma levels increase to a C_{max} at day 32, then decrease to near zero levels after day 60. The main phase of systemic drug exposure occurs between weeks 4-6, consistent with the *in vitro* release pattern. **Conclusion.** Risperidone microspheres are the first application of a long-acting injectable atypical antipsychotic. The formulation shows both *in vitro* and *in vivo* prolonged and predictable release of risperidone, compatible with a 2-week injection interval, and is associated with minimal pain.